# Reverse Cardio-Oncology

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# Reverse Cardio-Oncology: Cancer Development in Patients With Cardiovascular Disease

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Overwhelming epidemiological evidence demonstrate that cardiovascular disease and cancer represent major health burdens in the United States, and they are the leading causes of mortality.[1] According to the National Center for Health Statistics and the Centers for Disease Control and Prevention, 616 828 of a total 2 471 984 deaths were caused by cardiovascular disease and another 134 148 were caused by cerebrovascular disease.[2] Numbers from the American Cancer Society reveal that ≈17 million Americans have a history of cancer[3] (representing 5% of the total US population) and ≈1.7 million new cases are predicted to be diagnosed in 2019. Moreover, ≈660 880 Americans are expected to die of cancer during 2019, which corresponds to 1660 deaths per day.[4] Undoubtedly, these numbers will further increase as the population ages.

Generally, cardiovascular disease and cancer are viewed as 2 distinct disease entities. The appreciation that cancer and the cardiovascular disease may coincide mostly comes from cardiologists who care for patients with cardiovascular disease because of anticancer treatments (cardio-oncologists).[5,6] Other examples where cancer and cardiovascular disease meet are cardiac neoplasm or when cancer itself causes cardiovascular disease, but these are less common. The substantial increase in the number of cancer survivors and the spectacular increase in new cancer therapies, often causing cardiovascular complications, resulted in the foundation of a new discipline called cardio-oncology.[7,8] This subspecialty of cardiology establishes primary and secondary risk approaches through surveillance as well as interventions to stratify and diminish cardiovascular risk, to preclude cardiovascular toxicity and its progression, and to manage the adverse effects of anticancer treatments.[7,8]

Less appreciated are potential links between existing cardiovascular disorders and subsequent malignancy, demonstrating that patients with cardiovascular disease have higher cancer risk compared with individuals from the general population. Consequently, "reverse cardio-oncology" has started to attract more attention and called for awareness among physicians for the increased cancer risk in patients with cardiovascular disease.[9–12] It has been suggested that these 2 disease entities share mutual risk factors, such as obesity, diabetes mellitus, alcoholism, and tobacco, which may explain, at least in part, concurrent manifestation.[1,11,12] In addition, numerous ancillary mechanisms and pathways associated with cardiovascular disease were shown to be involved in cancer pathogenesis. Hence, further studies are needed to confirm and characterize the shared pathophysiological pathways between cardiovascular disease and cancer.[9,11,12] As for now, clinicians should be aware of the increased risk and establish recommendations and guidelines for early diagnosis of malignancy, also and maybe even stronger so among patients with cardiovascular disease.

This review focuses on reverse cardio-oncology and highlights clinical studies, meta-analyses, and cohorts that have evaluated cancer risk in patients with cardiovascular disease and the risk associated with treatments of cardiovascular disease. In addition, this article summarizes mechanisms of actions that mediate the cross talk between cancer and cardiovascular disease.

## Incidence of Cancer in Patients With Cardiovascular Diseases

The association between cardiovascular disease and cancer is not a novel concept.[11–13] In the past few decades, numerous studies have reported connections between cancer and hypertension, thromboembolism/stroke, atrial fibrillation (AF), atherosclerotic cardiovascular disease, myocardial infarction, and heart failure. Nevertheless, most evidence

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stems from retrospective analyses with mostly noncausal relationships. In addition, available evidence could be skewed toward positive associations caused by publication bias. Because of the potential implications of this concept for clinicians, and its repercussions for patients with cardiovascular disease, the following section aims to summarize previous studies and to present a critical viewpoint of their findings.

## Association Between Hypertension and Cancer Incidence

Several studies have hinted toward an association between hypertension and cancer incidence. A prospective cohort study showed that high blood pressure was associated with cancer incidence and cancer mortality, but this association was sturdier in men than in women.[14] On the basis of 18 studies, a meta-analysis demonstrated a 1.6-fold increase in the risk of renal cell carcinoma in participants with hypertension.[15] Another study reported a 5% and 7% higher risk for kidney cancer per every 10–mm Hg higher systolic blood pressure and diastolic blood pressure, respectively.[16] Moreover, a positive correlation between hypertension and risk of colorectal cancer was estimated, with an 11% higher risk in individuals with hypertension.[16] On the basis of a meta-analysis of 13 prospective studies, hypertension was linked to a 7% higher risk of total breast cancer.[16,17] Association between hypertension and risk of prostate cancer was evaluated in a meta-analysis that used 21 cohort and case-control studies. Investigators reported a statistically significant 8% higher risk. However, this report did not take into account individual study design and quality.[18] Furthermore, positive associations were observed between hypertension and risk of other cancers, including endometrial cancer, squamous cell carcinoma, esophageal adenocarcinoma, and liver cancer.[16] However, these meta-analyses could not include a large number of prospective studies, and most of them were performed without comprehensive multivariable adjustments, which raises concerns about the validity of these findings. There have been additional meta-analyses for endometrial cancer, but their conclusions were shaped without taking into account the study design.[19,20] Finally, no associations were observed between hypertension or blood pressure and risk of other cancers (namely, lung, cervix, brain, bladder, pancreas, stomach, and gallbladder).[16]

The safety of antihypertensive drugs with regard to cancer incidence has been debated. Many studies and meta-analyses have evaluated the carcinogenic potential of antihypertensive drugs. In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), participants were randomly assigned to receive chlorthalidone (diuretic treatment), amlodipine (calcium channel blocker), or lisinopril (angiotensin-converting enzyme inhibitor). The investigators of ALLHAT evaluated the clinical outcomes by antihypertensive treatment group and found that the 6-year rate of cancer was ≈10 per 100 people in the 3 groups. Also, cancer was the main noncardiovascular cause of death among patients treated with chlorthalidone, amlodipine, and lisinopril.[21] Moreover, candesartan, an angiotensin receptor blocker tested for its effectivity in heart failure in the Candesartan Heart Failure Assessment of Reduction in Mortality and Morbidity program, has been linked to increased cancer risk. Of the 371 noncardiovascular deaths, 145 were cancer related. It was implied that death attributed to cancer was more frequent in the candesartan group.[22] In contrast, other meta-analyses (comprising 70 randomized controlled trials) did not report any difference in cancer incidence and cancer mortality with antihypertensive treatments (ARBs [Angiotensin Receptor Blockers], angiotensin-converting enzyme inhibitors, β blockers, and diuretics) versus placebo. However, a slight increase in cancer risk was observed when angiotensin-converting enzyme inhibitor and ARB were administrated together.[23] The inconsistencies between meta-analyses could be caused by bias, such as selection bias, which may lead to inaccurate deductions. Evaluating the link between antihypertensive treatments and cancer is critical, considering the difficulty of ruling out the effects of competing risks. Today, millions of patients with hypertension are treated with antihypertensive drugs. Therefore, antihypertensive medications and management require more consideration as they may influence cancer risk independent of hypertension or elevated blood pressures.

## Cancer Prevalence Among Stroke Survivors and Patients With Thromboembolism

Many studies have reported a high prevalence of cancer deaths among patients who had a stroke.[24] The analyses of 3 large cohorts (the OSCP [Oxfordshire Community Stroke Project], the Lothian Stroke Register, and the IST [International Stroke Trial]) demonstrated that 38% of deaths were secondary to cancer.[24,25] Furthermore, analyses of the data that were collected as part of the VISP (Vitamin Intervention for Stroke Prevention) study demonstrated a higher annual rate of age-adjusted cancer incidence among ischemic stroke survivors compared with those of the general population.[24] This increase was comparable to the slightly higher risk of cancer in patients with pulmonary embolism and venous thrombosis.[26–28] Previously, the Swedish Inpatient Register was used to measure cancer incidence among 61 998 patients admitted to the hospital between the years 1965 and 1983 for venous thromboembolism. None of these patients had previously diagnosed cancer. The general conclusion was that venous thromboembolism could be a clear marker of cancer risk, and this assumption was based on the fact that 4% of cohort patients were diagnosed for

cancer at the time of the first admission, or during the first year.[28] Although several cohorts showed a continuous increase of cancer risk for as long as 10 years after the diagnosis of venous thromboembolism, others demonstrated a decline in cancer rates after 6 months. This inconsistency may be caused by the difference in cancer diagnosis strategies. Another explanation could be the size of the studies; some were larger, population based, and hospital record based, and others were smaller and observational.[29] Further research would be needed to evaluate the correlation between stroke or venous thromboembolism and cancer, and new guidelines should be established for cancer screening in diagnosed patients.

As for antithrombotic drugs, several studies have reported their antitumor benefits. Case-control studies suggested that the use of warfarin may be associated with a reduced incidence of urogenital malignancies.[30,31] It is hypothesized that the potential antineoplastic effects of warfarin may be explained by its interaction with mediators of tumor invasion, such as tissue factor, factor VIIa, and urokinase receptors.[27] Furthermore, cancer was detected in 15.8% of patients who were treated for 6 weeks with oral anticoagulants and in 10.3% of patients who were treated for 6 months, but the investigators did not demonstrate the percentage of cancer among untreated participants.[27] Findings generated from another observational study showed that shorter duration of anticoagulation was associated with a higher cancer risk compared with longer duration of anticoagulant administration, which complements the previous findings.[29] Data from randomized trials were used to assess the effects of aspirin on risks of vascular and cancer events, according to dose and body weight. The administration of 75 to 100 mg of aspirin reduced risk of colorectal cancer in participants with a body weight <70 kg, but this reduction was not observed in people weighing ≥70 kg. However, with higher aspirin doses (≥325 mg), similar benefits were observed in individuals weighing up to 80 kg.[32] Aspirin did not affect the total number of cancer deaths. Nevertheless, the investigators demonstrated that aspirin diminished cancer-related deaths, after 5 years of follow-up, in individuals weighing <70 kg. The ASPREE (Aspirin in Reducing Events in the Elderly) trial was conducted in the United States and Australia to assess the effect of aspirin on longevity and all-cause of mortality in healthy elderly individuals.[33] In total, 19 114 participants were randomly assigned to receive 100 mg aspirin or placebo. The investigators found that cancer was the main cause of death in both groups and reported a higher risk of cancer-related death in the aspirin group compared with the placebo group (6.7 versus 5.1 events per 1000 person-years). In addition, the percentages of cancer-death (cancer-death/all causes of death) were shown to be higher in the aspiring group in comparison to the placebo group (52.9% versus 46%). These findings contradict the findings of previous meta-analyses in which aspirin was shown to have a protective effect on cancer-related mortality. It is still unclear whether aspirin has an early or delayed anticancer effect.[33] Maybe cancer physiological features and their molecular patterns differ among age and weight groups. It has been shown that aspirin could affect several aspects of cancer, such as inflammation, angiogenesis, metastasis, and tumor growth.[34] Further assessments are still needed to evaluate the mechanisms by which these drugs exert their anticancer effects.

## AF: Is a Potential Risk Marker for Cancer

AF is the most common form of cardiac arrhythmia,[35,36] and it is linked to other major cardiovascular complications.[37–39] Patients with AF are exposed to a substantial risk of death because of noncardiovascular causes.[40] In 1994, the first report of AF preceding colon cancer was published.[41] Twenty years later, the registry study of all Danish patients was published and showed that participants had a 2.5% absolute risk of cancer in the first 3 months after the diagnosis of AF.[42] The investigators found that 57% of the cancer cases were metastatic at the time of diagnosis, which led them to conclude that AF, to some extent, may be regarded as a marker for occult cancer.[42] The RE-LY (Randomized Evaluation Long-Term Anticoagulant Therapy Study) showed that more than one third of all deaths among participants with AF were caused by noncardiovascular reasons, and the malignant tumors were a main cause of these mortalities.[40,43] Also, the relation between AF and cancer was inspected in the "WHS (Women's Health Study)",[43] which is a randomized clinical study that assessed the effects of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular diseases.[44,45] The investigators found that 10% of participants with new-onset AF developed subsequent cancer.[43] Moreover, AF was substantially associated with cancer occurrence, and this correlation was not affected by the administration of aspirin nor by the administration of vitamin E.[43] The risk of cancer was notably higher in women with paroxysmal or nonparoxysmal AF. The multivariable-adjusted association between new-onset AF and colon cancer was statistically significant, but this was not the case for lung and breast cancers.[43] In 2018, a Danish population-based cohort study evaluated the correlation between AF and risk of cancer in 26 222 men and 28 879 women free of AF and cancer at baseline.[46] A total of 15% of men and 11.1% of women with new-onset AF had a subsequent cancer.[46] During the 12-year period after the diagnosis of AF, 23.3% of men and 19.1% of women were diagnosed with cancer. It was also noted that for both sexes, the incidence rate of any type of cancer (any type of cancer or lung and colorectal cancer) was higher during the first 3 months after the diagnosis of AF.[46]

There were several attempts to solve the question as to whether AF can be considered as a risk factor for cancer. Considering the strength of this statement, one should keep in mind that the term "risk factor" refers to a causal connection between outcome and exposure. The mechanisms mediating these associations are perhaps multifactorial and comprise common risk factors and pathways.[47]

The updated guidelines for the management of patients with AF, established by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society, recommend the use of several anticoagulants, such as warfarin, dabigatran, rivaroxaban, and apixaban.[48] The RE-LY evaluated 2 fixed doses of dabigatran, which is a direct thrombin inhibitor. The doses were blindly administrated, and with open-label use of warfarin in participants who had AF.[40] Data on mortality showed that 61.41% of deaths were because of cardiovascular causes and 13.93% were cancer-related deaths. Also, cancer was the number one noncardiovascular cause of death in the dabigatran and warfarin groups.[40] In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), individuals with nonvalvular AF were randomized to rivaroxaban or dose-adjusted warfarin. Rivaroxaban and warfarin groups did not exhibit a significant difference in all-cause mortality. Once again, malignancy-related mortalities were the highest among the noncardiovascular mortalities in both groups.[49] The ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial randomized participants with AF to apixaban or warfarin. Apixaban was superior to warfarin in preventing stroke events, and also in showing less bleeding and lower mortality.[50] Also, malignancy was the most common cause of death among noncardiovascular deaths in the ARISTOTLE trial (21%).[51] Considering the fact that cancer is the leading noncardiovascular cause of mortality in most of the trials, the safety of the drugs used for the management of AF should be assessed continuously to avoid any further health burden.

## Cancer Prevalence in Patients With Atherosclerotic Cardiovascular Diseases and Myocardial Infarction

In the modern era, cardiac care in patients with atherosclerotic cardiovascular diseases has markedly improved.[52] Invasive and pharmaceutical strategies, adopted by the long-term cardiovascular care systems, have resulted in a better prevention of atherosclerotic events and their complications.[53] Trends in causes of mortality in patients after percutaneous coronary interventions presented a shift from cardiovascular to noncardiovascular mortality in patients treated with percutaneous coronary intervention. This increase in noncardiovascular mortality was attributed to cancer and other diseases.[54] On the basis of the ARIC (Atherosclerotic Risk in Communities) study, lower cancer prevalence could be linked to guidelines for the prevention of atherosclerosis, which means that there are many common risk factors for cancer and atherosclerotic cardiovascular alterations.[55] A total of 32 095 participants with cardiovascular diseases were enrolled in the SHIP (Sakakibara Health Integrative Profile) cohort study.[52] To evaluate the incidence of cancer and mortality in patients with atherosclerosis, participants were segregated on the basis of the presence and absence of atherosclerotic cardiovascular diseases (namely, aortic diseases, coronary artery diseases, and peripheral artery diseases). Cancer prevalence (5% versus 2%) and mortality (6% versus 3%) were >2-fold higher in patients with atherosclerotic cardiovascular disease than in patients with nonatherosclerotic cardiovascular diseases.[52] These findings suggest atherosclerosis as a risk factor for cancer and a marker of poor prognosis.[52] Ultrasound and autopsy assessments demonstrated a strong correlation between atherosclerosis in the carotid and coronary arteries.[56,57] Moreover, the incidence rates of cancer and death were evaluated in participants with myocardial infarction from data of 4 Danish registries: The Danish Civil Registration System registry, the NPR (Danish National Patient Registry), the National Causes of Death Registry, and the Danish National Prescription Registry.[58] All age groups showed that the prevalence rates of cancer and death were higher among participants with myocardial infarction.[58] The authors reported the highest incidence of cancer and death during the first year after the diagnosis of myocardial infarction. In addition, the youngest age group (30–54 years) exhibited the highest prevalence of colorectal, lung, and urinary track cancers. However, the risk of these cancers was decreased in older groups (55–69 and 70–99 years).[58] Recent study provided striking insights about the connection between myocardial infarction–induced heart failure and the intestinal tumor progression in C57BL/6J-ApcMin/J mice, which are predisposed to developing precancerous intestinal tumors.[59] Six weeks after the induction of myocardial infarction or the sham surgery, the investigators reported more and larger intestinal polyps in C57BL/6J-ApcMin/J mice with failing hearts.[59] At the cellular level, treating HT-29 with α-1-antichymotrypsin and α-1-antitrypsin, 2 proteins overexpressed in the myocardium of C57BL/6J-ApcMin/J mice with heart failure, resulted in an increased proliferation of these colorectal cancer cells.[59] Finally, the authors showed that heart failure and inflammation markers were associated with cancer incidence among participants with heart failure from the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study.[59]

There are many available antiatherosclerosis treatments, such as statins and antiplatelet agents.[60] The relation

between statins and cancer incidence is still under debate, although heavily studied. However, the anti-inflammatory properties of statins could be a starting point to evaluate any potential link with cancer prevention.[11] Revolution and advances in pharmacological treatments and percutaneous coronary intervention resulted in better disease management and significantly decreased mortality.[61,62] In the United States, >85% of coronary stents used are drug-eluting stents.[63] In an integrated analysis on patients recruited in 4 trials,[64] patients were randomly assigned to receive a sirolimus-eluting or a bare-metal stent. Around 60% of deaths were caused by noncardiovascular causes, and cancer was among the most frequent noncardiovascular cause of death.[64] Moreover, a meta-analysis of 17 stent trials revealed that cancer, stroke, and infectious diseases were the main noncardiovascular causes of mortality.[65] These findings suggest a possible connection between stenting and cancer-related mortality and serve as a basis for further delineations.

To conclude, the epidemiological studies above present interesting evidence of associations between cardiovascular disease and the risk of incident cancer. Although these findings certainly raise significant scientific questions and are of considerable hypothesis-generating value, it is important to critically assess and highlight their limitations and validity. Most evidence originates from associations identified in retrospectives analyses. This has inherent limitations in that causality is not guaranteed and that retrospective analyses are hampered by their original design not being powered toward specific cancer outcomes. In addition, the reported potential procancer and anticancer effects of cardiovascular medication constitute contradictory information because the studies reporting them were not necessarily concordant with each other, even when the same treatment was being studied. As such, future targeted and independent studies are required before definitive conclusions can be drawn. Last, to eventually reach clinically relevant and applicable conclusions, translation of the shared risk factors and biological processes common to both cancer and cardiovascular disease to clinical significance is imperative.

## Potential Mediators of the Cross Talk Between Cardiovascular Disease and Cancer

Apart from the above-mentioned potential epidemiological association, shared biological mechanisms and risk factors may explain the link between cardiovascular disease and cancer. Among others, pathways related to inflammation, clonal hematopoiesis, and hypoxia, as well as circulating microRNAs, extracellular vesicles, and mediators of cardiac origin are of interest in this regard. Advancements in our scientific understanding behind the interactions between cardiovascular disease and cancer and the exact role of all the aforementioned factors in this cross talk could potentially lead to mechanistic insights that can guide future therapeutic research and clinical decision making. However, the unification of the available literature into a quintessential distilled essence poses considerable challenges, considering the heterogeneity and disparity of experimental designs, end points, and scientific messages of the available literature. Therefore, the following section aims to summarize current knowledge to bridge past and future research approaches.

## Inflammation as a Key Mediator of the Pathophysiological Connection Between Cardiovascular Disease and Cancer

Inflammatory pathways contribute to the pathophysiological features of cardiovascular disease and cancer, and they are involved in the initiation, progression, and poor prognosis of the 2 diseases.[66] Recent studies emphasized the involvement of many inflammatory mediators in the EMT (epithelial to mesenchymal transition), which is as a key step toward malignant transformation and metastatic behavior.[66,67] In the context of myocardial infarction, necrotic cells intensify inflammatory responses by releasing danger signals.[68] Downstream signaling comprises the overactivation of mitogen-activated protein kinases and the abnormal stimulation of the nuclear factor-κB. Subsequent overexpression of proinflammatory genes (cytokines and chemokines) triggers inflammatory cells, causes oxidative damage and stress, causes DNA alterations, and modifies the tissue microenvironment, which can lead to malignant transformation in cells.[69] Ischemia induces several cytokines, including tumor necrosis factor, which is a potent activator of nuclear factor-κB, a primary mediator of inflammation in cancer.[70,71] Recently, the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) has reported promising results, validating inflammation as a worthwhile target for cardiovascular disease management.[72] The investigators showed that canakinumab, an interleukin-1β neutralizing monoclonal antibody, diminished cardiovascular events in treated participants.[73] Also, total cancer mortality and lung cancer fatalities were substantially lower in the canakinumab group than in the placebo group.[72] In addition, it has been shown that heart failure–associated inflammatory markers, including C-reactive protein, had a clear predictive value independently of cancer risk factors.[59] The previously discussed α-1-antichymotrypsin is strongly related to systemic inflammation, and it is one of the proteins that were elevated in patients with heart failure.[59,74,75] The same group showed that α-1-antichymotrypsin induces colorectal cancer cell (HT-29) proliferation and tumor growth via protein kinase B pathways. The investigators reported a significant phosphorylation of protein kinase B and ribosomal protein S6 in HT-29 treated with α-1-antichymotrypsin.[59] Assessing

inflammation as a mechanistic link between the 2 diseases could offer numerous opportunities and innovative solutions to reduce their heavy burden.

## Clonal Hematopoiesis: A Newly Recognized Link Between Cardiovascular Disease and Cancer

Somatic genetic mutations are an unescapable consequence of aging.[76,77] This is especially true in the highly proliferative hematopoietic tissues.[78] Genetic alterations in bone marrow hematopoietic stem cells result in the generation of mutated leukocyte clones in the peripheral blood.[79] This state is not cancer, but could be considered as a step toward leukemia, which leads to the term "clonal hematopoiesis of indeterminate potential" (CHiP). In fact, the transition to leukemia necessitates 2 or 3 consecutive mutations in cancer driver genes within the same clone.[79] Mutations in >20 genes have been shown to be involved in the transition to myelodysplastic syndrome and acute myeloid leukemia.[79] The analysis of bone marrow–derived mononuclear cells isolated from patients showed that somatic mutations in hematopoietic cells, particularly in the genes Ten-Eleven Translocation-2 (TET2) and DNA methyltransferase 3A, were associated with the development and poor prognosis of heart failure.[80] Another study found that mutations in TET2, Janus kinase 2, and additional sex combs-like were associated with early-onset myocardial infarction.[81] The absence of the CHiP driver gene TET2 in mice resulted in accelerated atherosclerosis progression and higher predisposition to cardiac dysfunction.[81,82] Experiments in murine models reported an elevated IL-1β activity in the presence of CHiP mutations.[81,83] Interestingly, dysfunctional TET2 was linked to the activation of the cytoplasmic supramolecular assembly Nod-like receptor protein 3 inflammasome and inflammatory cytokine interleukin-6.[84,85] It has been suggested that inflammatory mediators, like interleukin-1β, could affect cardiovascular and oncological outcomes in individuals with CHiP.[86] The CANTOS revealed that canakinumab, an interleukin-1β antibody, decreased cardiovascular incidence.[87] Interestingly, CHiP-positive patients (with TET2 mutations) in the CANTOS benefitted better to canakinumab than participants without CHiP.[88] In addition, the administration of higher dosages of canakinumab resulted in reduced lung cancer prevalence and less cancer mortality.[72] Furthermore, Nod-like receptor protein 3 and interleukin-1β can promote tumor growth and metastasis in several cancer types, such as breast cancer, lung cancer, and melanoma.[89] These findings suggest that CHiP is a new link between the 2 major diseases. The mechanisms that underlie this correlation include common mutations in the oncogenic genes and inflammatory factors secreted by the mutant leukocytes, as depicted in Figure 1. Currently, we have more questions than answers and further investigations are needed to identify the aspects of this correlation.

## Hypoxia Caused by Cardiovascular Disease and Its Role in Cancer Progression

Hypoxia in patients with cardiovascular disease could be triggered by insufficient blood flow, hypoxemia, and microvascular-endothelial alterations.[5] At the molecular level, hypoxia-inducible factor 1 is stabilized in response to myocardial ischemia or infarction.[90] Hypoxia-inducible factor 1 is a transcription factor that induces transcription of vascular

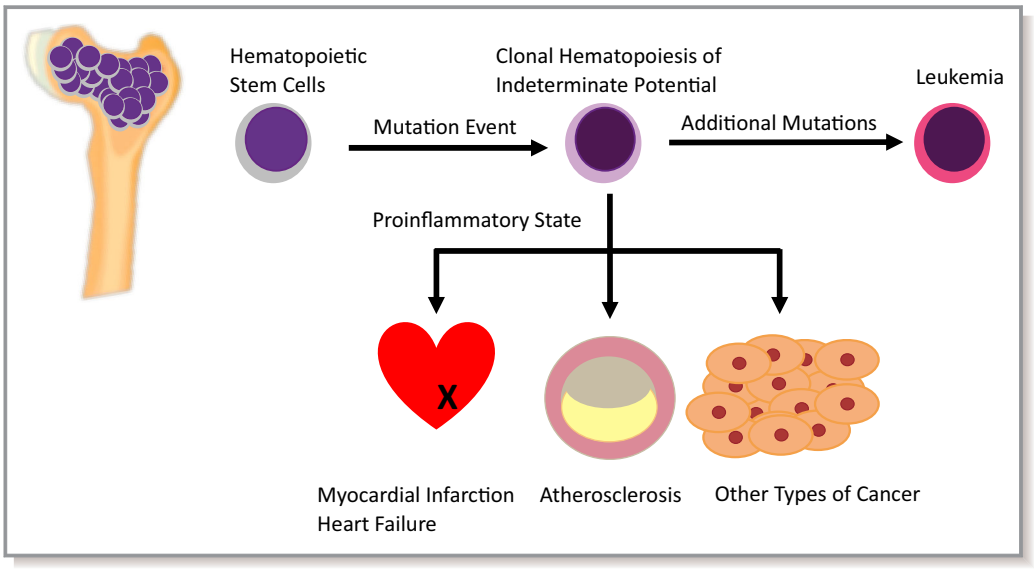


**Figure 1.** Graphic illustration showing somatic mutations in hematopoietic stem cells as a common path for cancer and cardiovascular disease.

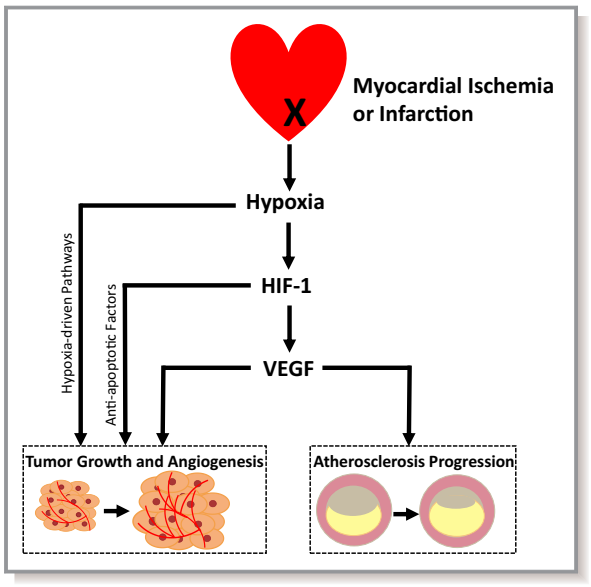


**Figure 2.** Theoretical depiction of the mechanisms by which hypoxia contributes to cancer growth and angiogenesis. HIF-1 indicates hypoxia-inducible factor 1; VEGF, vascular endothelial growth factor.

endothelial growth factor and is involved in atherosclerosis progression.[91] As discussed in another review,[5] in the context of cancer, hypoxia-inducible factor 1 stimulates tumor growth and progression by increasing the expression of antiapoptotic factors and boosting angiogenesis.[92–94] Besides, vascular endothelial growth factor is a key mediator of angiogenesis in cancer.[95] The pathogenesis of several cancer types, including multiple melanoma and breast cancer, involves numerous hypoxia-triggered pathways.[96,97] Therefore, hypoxia-driven mechanisms stimulated by cardiovascular disease could result in malignancies, which makes them another significant therapeutic target (Figure 2).

## Circulating Factors Linking Cardiovascular Disease to Cancer

Beside recognizing new biomarkers, it is essential to understand their function and evaluate the mechanisms by which they affect the homeostasis in tissues. Under pathological conditions, multiple cardiac cells, such as fibroblasts, cardiomyocytes, and smooth muscle cells, secrete "cardiokines" into the circulation (Figure 3).[98] Because of their endocrine and paracrine effects, the initiation and progression of many diseases could be mediated by these cardiac factors. In ischemic hearts, cardiomyocytes generate many cardiac factors, including Apelin.[99] The latter readapts actin cytoskeleton organization and increases the level of membrane type 1 matrix metalloprotease, which boosts proteolytic capacities and migration abilities in colon cancer cells.[100] After ischemia or reperfusion (ischemia-reperfusion injury), fibroblasts produce fibroblast growth factors to enhance cell survival and cardiac recovery.[101,102] The fibroblast growth factor system mediates epithelial to mesenchymal transition and promotes tumor angiogenesis and progression.[103] Furthermore, ventricular hypertrophy is strongly associated with the production of another cardiokine, called osteopontin, which is mainly produced by cardiomyocytes.[104] As demonstrated in another review, osteopontin has been shown to promote the development of many solid organ tumors via different pathways.[105] Atherosclerotic carotid plaques secrete growth arrest–specific gene 6, which stimulates survival and mobility of vascular smooth muscle cells and promotes their accumulation in the atherosclerotic plaque.[106] On the basis of in vitro studies, growth arrest–specific gene 6 promotes EMT and cancer invasiveness by activating mitogen-activated protein kinase and Slug pathways.[107] Under hemodynamic stress, cardiomyocytes secrete atrial natriuretic peptide.[108] In contrast to the other cardiokines discussed in this review, atrial natriuretic peptide has been demonstrated to have anticancer effects by targeting many signaling pathways, such as c-FOS and c-JUN, rat sarcoma, mitogen protein kinase 1/2, and extracellular signal-regulated kinases 1/2.[108] In addition to cardiokines, the cardiovascular system secretes other factors and genetic materials, such as microRNAs.

To date, circulating microRNAs have been identified as biomarkers for diagnostic and prognostic purposes.[109] MicroRNAs modulate a variety of cellular and biological processes, including cell proliferation, apoptosis, stemness, senescence, epithelial to mesenchymal transition, and inflammation.[110] Therefore, microRNAs are involved in the pathogenesis of many human diseases, such as heart diseases,[111] vascular diseases,[112] and cancers.[113] In a context-dependent manner, the same microRNAs can function as a cardio-microRNA, angio-microRNA, or onco-microRNA.[110] On the basis of previous experimental screening of microRNA reports and validation techniques using next-generation sequencing, 4 microRNAs were identified as cardio-microRNAs as they were upregulated in human heart disease, and they were as follows: microRNA-24, microRNA-125b, microRNA-195, and microRNA-214.[114–118] Interestingly, the same 4 microRNAs were reported as oncogenic or tumor suppressors in several cancer subtypes, including myeloid leukemia, pancreatic cancer, lung adenocarcinoma, and prostate cancer.[110] Therefore, cardio-microRNAs are potential connectors between cardiovascular disease and tumors, which makes them central therapeutic targets. Establishing databases of circulating microRNAs from cancer and cardiovascular disease is required to bridge the gap between the 2 fields. The circulating microRNAs could be conjugated with the high-density lipoprotein and Argonaute 2 protein or transported within extracellular vesicles (exosomes and microvesicles) (Figure 3).[119–122]

In terms of contents, extracellular vesicles are loaded with distinct components of lipids (phospholipids), proteins (membrane receptors, enzymes, regulatory proteins, and adhesion molecules), genetic material (nucleic acids, mRNAs, and microRNAs), cytokines, chemokines, and growth factors.[123] Extracellular vesicles and their contents are a rapidly growing area of research in cancer because of their contribution to oncogenesis, cancer invasiveness, epithelial to mesenchymal transition, and metastasis, and resistance to anticancer chemotherapy.[124] Extracellular vesicles involved in cardiovascular diseases share features with the ones that mediate cancer progression and development (Figure 3).[124] The study by Ohtsuka and colleagues demonstrated that platelet-derived microvesicles, obtained from atherosclerotic patients, promote neovascularization by secreting the regulated upon activation normal T-cell expressed and secreted.[125] The latter was already demonstrated to be involved in gastric cancer metastasis.[126] Regulated upon activation normal T-cell expressed and secreted may contribute to breast cancer progression by promoting monocyte migration into tumor sites. Also, regulated upon activation normal T-cell expressed and secreted induces the expression of matrix metalloproteinase 9 and stimulates vascularity.[127] These data indicate that extracellular vesicles constitute another connector between cardiovascular disease and cancer. Detecting, analyzing, and validating the content and the features of extracellular vesicles are required to reach an effective therapeutic application of these particles into the clinical field.

## Clinical Implications

Clinical trial data, meta-analyses, and cohort studies consistently confirmed the correlation between cardiovascular disease and cancer. This serves as a basis for further investigations to understand mechanisms that mediate this connection and to identify new therapeutic targets. In the next few years, we expect that the field of cardio-oncology will evolve in innovative ways with breakthroughs that will translate into their use for diagnosis, primary prevention, treatment, and other clinically relevant end points (Figure 4).

However, inconsistencies between the outcomes of the published studies are a limitation, and generation of more high-quality data is needed. The apparent discrepancies may be caused by differences in cancer and cardiovascular diagnoses, guidelines, and strategies. Another reason could be the size and design of the various studies. Besides, cancer and cardiovascular disease are general terms that refer to large groups of heterogeneous diseases, which complicates analyses and interpretations of data. Unifying inclusion criteria, using stronger diagnostic guidelines, and performing meticulous end point adjudication will help to improve the quality of generated data. Also, clinical data registries should be established in more countries to provide tailored outcomes based on the characteristics of each population.

Clearly, intense collaborations between oncologists, hematologists, and cardiovascular specialists will be required to establish guidelines for cardio-oncology and reverse cardio-oncology. For instance, the study of CHiP detection involves

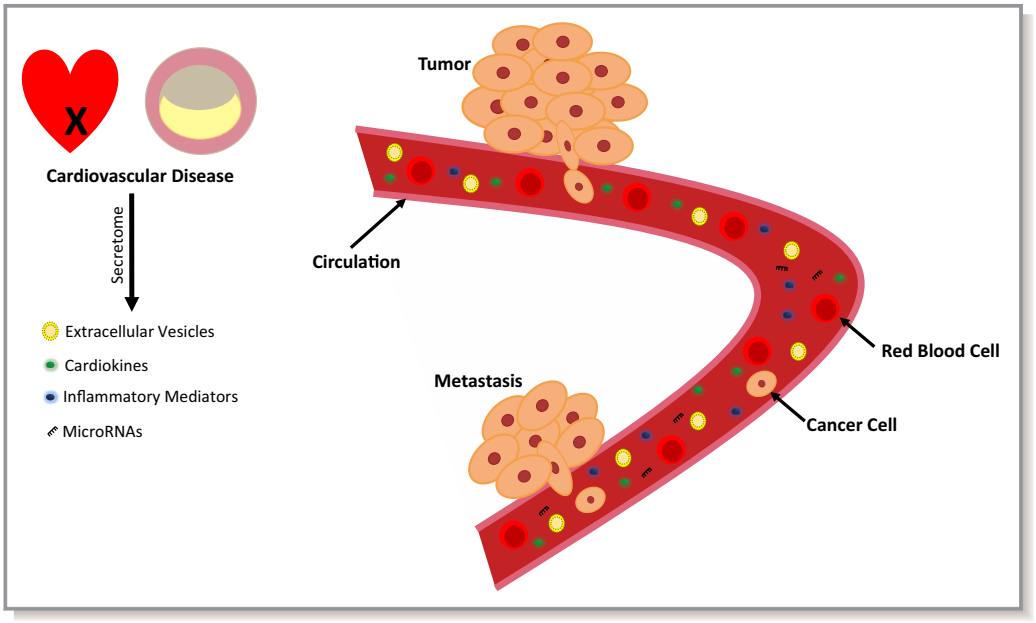


**Figure 3.** Theoretical depiction of cardiac secretome and its effect on tumor development, mobility, and metastasis.

expensive DNA sequencing techniques and stand-alone initiatives but will be costly and likely not feasible. However, in the near future, decreased cost of CHiP testing would allow screening of more individuals, furthering research and collaboration efforts.[79] In addition to clinical data, we anticipate that identifying and measuring biomarkers will be essential to establish clinical prediction models and algorithms to evaluate the risk of cancer among patients with cardiovascular diseases. Moreover, the use of cardiovascular disease drugs requires more attention as it may impact cancer risk independent of cardiovascular disease. Accordingly, healthcare professionals should modify cardiovascular disease management guidelines and establish primary and secondary risk approaches through surveillance as well as interventions in a concerted effort to reduce cancer risk, manage the adverse effects of cardiovascular treatments, and allow optimal cardiovascular and cancer outcomes.

In summary, although classic cardio-oncology focuses on cardiovascular risk in patients with current or treated cancer, reverse cardio-oncology deals with inherent cancer risk in patients with cardiovascular disease. Recent data have raised more awareness for this phenomenon. Shared risk factors, pathophysiological pathways, and treatments may explain the complex relation. Future studies should ensure precise phenotyping of both disease domains and help to identify risk assessment and treatment algorithms for patients.

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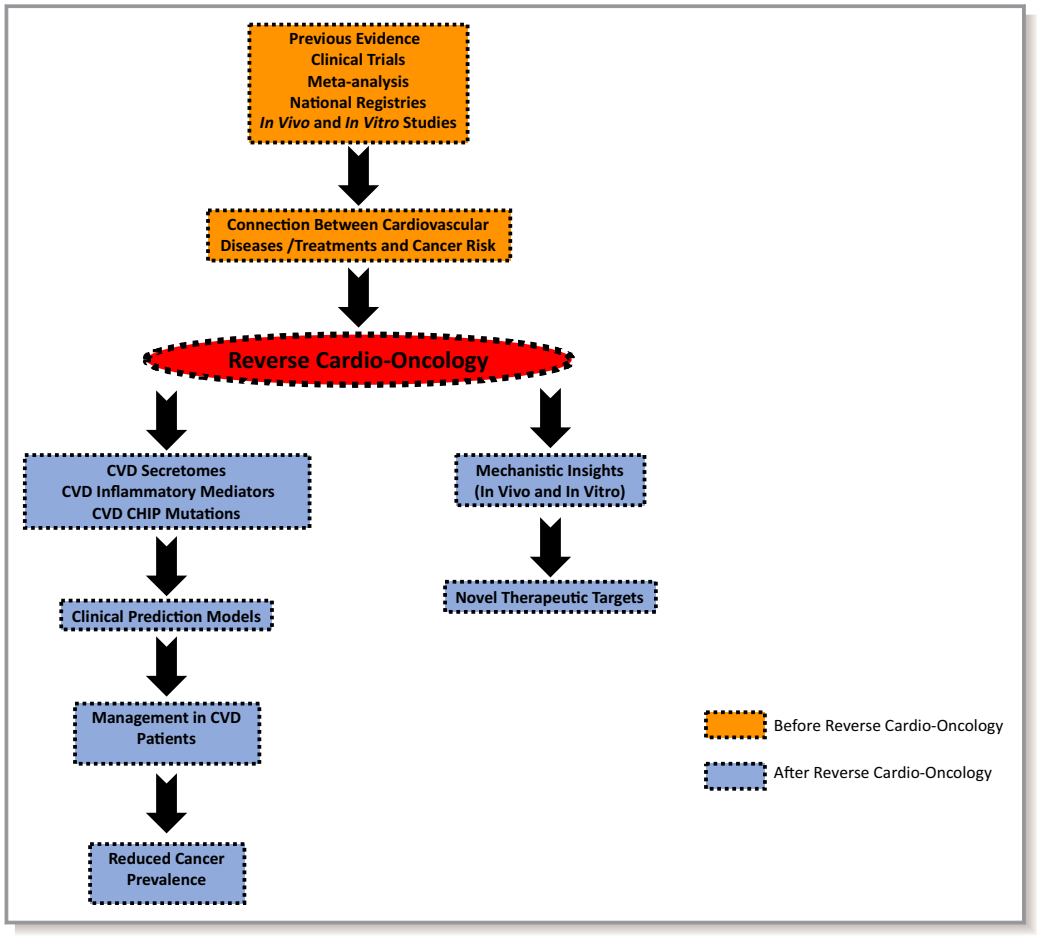


**Figure 4.** Illustration of the reverse cardio-oncology clinical end points. CHIP indicates clonal hematopoiesis of indeterminate potential; CVD, cardiovascular disease.

## Disclosures

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